

Supplementation of Long-Chain Fatty Acids with lactating Mammary Glands and Beef Cow has Potential Benefits

Abstract

G Protein-Coupled Receptor (GPCR) super family represents the largest protein family in the human genome. These receptors respond to various physiological ligands such as photons, odors, pheromones, hormones, ions, and small molecules including amines, amino acids to large peptides and steroids. GPCRs are involved in many biological responses and the target of around half of all conventional drugs. The physiological roles of Free Fatty Acids (FFAs), in particular, long-chain FFAs, are important for the development of many metabolic diseases including obesity, diabetes, and atherosclerosis. In the past half decade, deorphanization of several GPCRs has revealed that GPR40 and GPR120 sense the concentration of extracellular fatty acids. GPR40 and GPR120 are activated by long-chain FFAs. GPR40 is expressed in mammary epithelial cells and lactating mammary glands, and possesses strong proliferative and survival effects via an activation with unsaturated long-chain fatty acid. GPR120 is expressed in adipocytes and adipose tissues and plays an important role for FFAs-induced glucagon-like peptide-1. The objective of this review is to explore whether or not it is possible to enhance the yield of dairy milk and the quantity of fat marbling in beef by supplementing unsaturated The objective of this review is to explore whether or not it is possible to enhance the yield of dairy milk and the quantity of fat marbling in beef by supplementing unsaturated FFAs with lactating mammary glands.

Keywords: GPR40; GPR120; Unsaturated long-chain fatty acids; Lactating mammary glands; Marbling

Mini Review

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Abbreviations: GPCRs: G Protein-Coupled Receptors; LCFAs: long-Chain Fatty Acids; GLP-1: Glucagon-like Peptide-1; ERK: Extracellular Regulated Kinase; JNK: cJun N-terminal Kinases; PI3K: Phosphatidylinositol-3kinase; PTX: Pertussis Toxin; PUFA: Poly Unsaturated Fatty Acid; Glut: Glucose Transporter

Fatty Acid Receptors

We are writing this review, November 8, on whether or not it is possible to enhance the yield of dairy milk and the quantity of fat marbling in beef by supplementing unsaturated FFAs with lactating mammary glands. We've examined the effects of fatty acids on mammary epithelial cells and adipocytes including cow [1-3]. The ligands of two G Protein-Coupled Receptors (GPCRs), were recently identified as Long-Chain Fatty Acids (LCFAs) in the blood [4-6]. One is GPR40, which three different groups pointed out as being highly expressed in pancreatic islets, and particularly in pancreatic beta-cells secreting insulin [3-5]. Another is GPR120 [7]. This is exclusively expressed in the intestines, especially enteroendocrine cells, L-cells producing Glucagon-like Peptide-1 (GLP-1) [6]. GPR120 couples Gq/11 proteins and activates extracellular regulated kinase (ERK) 1/2, cJun N-terminal kinases (JNK), p38 and Phosphatidylinositol-3Kinase (PI3K)/Akt signaling pathway [8] (Figure 1 left portion). Both GPCRs play an essential role in LCFAs-induced secretion of each hormone. It is critical to understand how LCFAs affect cells and tissues through GPCRs.

Unsaturated Fatty Acid Enhances Proliferation and Survival in Mammary Epithelial Cells Via GPR40

Additionally, concurring with another group we and another group demonstrated that GPR40 functions in cell proliferation and survival through ERK 1/2 and PI3K/Akt signaling pathway [1,2,9,10] and its coupling manner to G protein is mainly dependent on Gi/o, which is Pertussis Toxin (PTX)-sensitive, and to lesser extent Gq/11 [1,7] (Figure 1 right portion). It is striking that unsaturated LCFA, but not saturated, possesses strong proliferative and survival effects on mammary epithelial cells, including bovine mammary epithelial cells [1,7]. This could potentially have an effect on the inhibition of apoptosis in lactating mammary glands, resulting in enhancement of the duration of lactation, the yield of milk production, and the quality of milk fat (Figure 1).

Unsaturated Fatty Acid Enhances Adipogenesis and Anabolism Via GPR120

In adipose tissue, Roh's group demonstrated that GPR120, but not GPR40, is exclusively expressed and its expression is induced through adipogenesis [3]. Furthermore, they also demonstrated that specific knocked-down GPR120 inhibits adipogenesis, indicating GPR120 plays an important role in adipogenesis and fat accumulations [3]. Indeed, in human and mouse studies, Poly Unsaturated Fatty Acid (PUFA) stimulates the Glucose Transporter (Glut) 4-dependent glucose uptake through GPR120, which is

de novo lipid synthesis and anabolism [11]. Taken together, intramuscular or intravenous infusion with LCFAs, especially if unsaturated, may contribute to the development of marbling in cows.

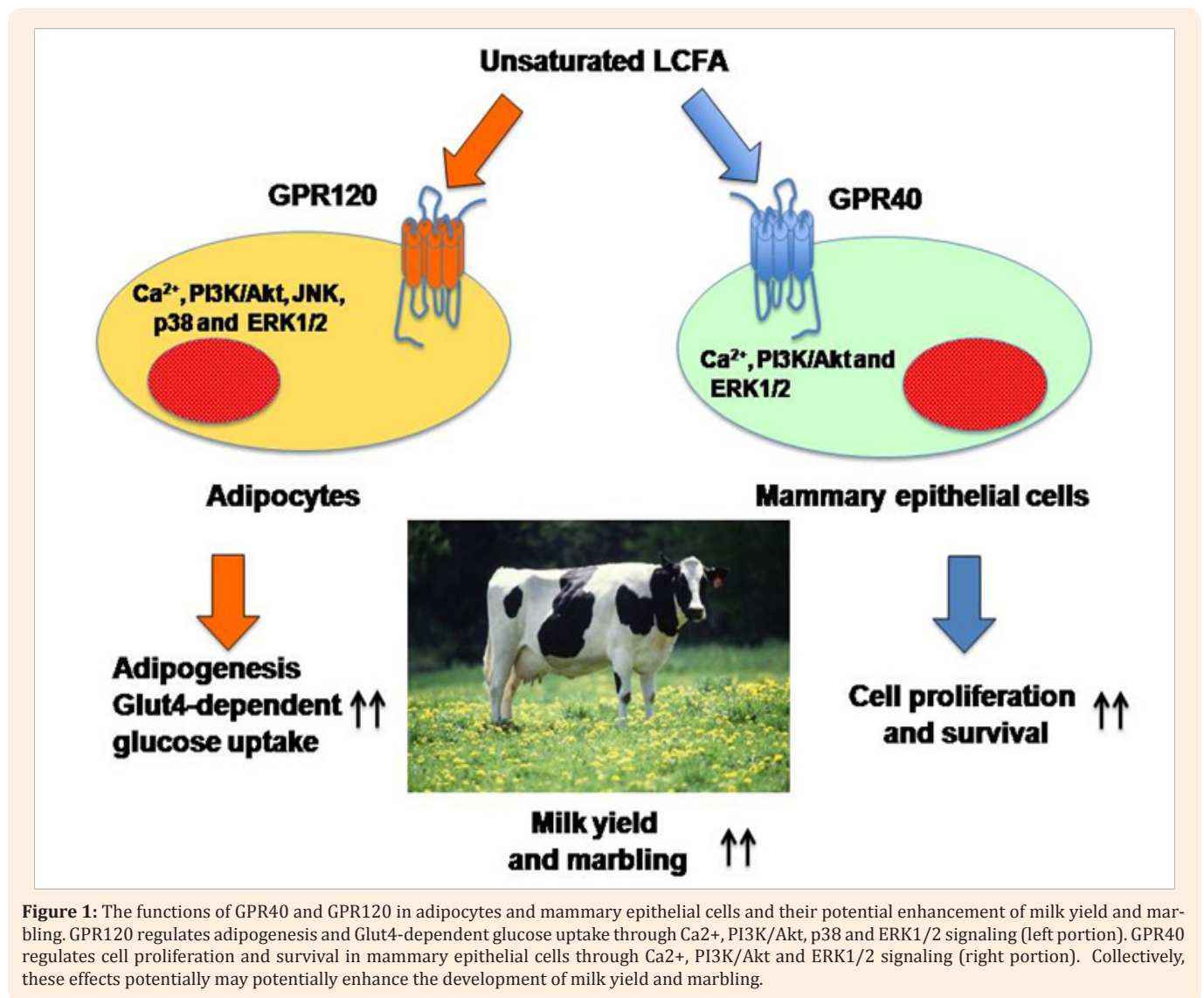


Figure 1: The functions of GPR40 and GPR120 in adipocytes and mammary epithelial cells and their potential enhancement of milk yield and marbling. GPR120 regulates adipogenesis and Glut4-dependent glucose uptake through Ca²⁺, PI3K/Akt, p38 and ERK1/2 signaling (left portion). GPR40 regulates cell proliferation and survival in mammary epithelial cells through Ca²⁺, PI3K/Akt and ERK1/2 signaling (right portion). Collectively, these effects potentially may potentially enhance the development of milk yield and marbling.

Perspective on Dairy and Beef Animal

Finally, we emphasize that the supplementation of milk and beef with LCFAs may potentially enhance milk yield and the quality and composition of marbling.

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References

1. Yonezawa T, Katoh K, Obara Y (2004) Existence of GPR40 functioning in a human breast cancer cell line, MCF-7. *Biochem Biophys Res Commun* 314(3): 805-809.

2. Yonezawa T, Haga S, Kobayashi Y, Katoh K, Obara Y (2008) Unsaturated fatty acids promote proliferation via ERK1/2 and Akt pathway in bovinemammary epithelial cells. *Biochem Biophys Res Commun* 367(4): 729-735.
3. Gotoh C, Hong YH, Iga T, Hishikawa D, Suzuki Y, et al. (2007) The regulation of adipogenesis through GPR120. *Biochem Biophys Res Commun* 354(2): 591-597.
4. Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, et al. (2003) Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 422(6928): 173-176.
5. Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, et al. (2003) The orphan G protein-coupled receptor GPR40 is activated

- by medium and long chain fatty acids. *J Biol Chem* 278(13): 11303-11311.
6. Kotarsky K, Nilsson NE, Flodgren E, Owman C, Olde B (2003) A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biophys Res Commun* 301(2): 406-410.
 7. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, et al. (2005) Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* 11(1): 90-94.
 8. Katsuma S, Hatae N, Yano T, Ruike Y, Kimura M, et al. (2005) Free fatty acids inhibit serum deprivation-induced apoptosis through GPR120 in a murine enteroendocrine cell line STC-1. *J Biol Chem* 280(20): 19507-19515.
 9. Hardy S, St-Onge GG, Joly E, Langelier Y, Prentki M (2005) Oleate promotes the proliferation of breast cancer cells via the G protein-coupled receptor GPR40. *J Biol Chem* 280(14): 13285-13291.
 10. Soto-Guzman A, Robledo T, Lopez-Perez M, Salazar EP (2008) Oleic acid induces ERK1/2 activation and AP-1 DNA binding activity through a mechanism involving Src kinase and EGFR transactivation in breast cancer cells. *Mol Cell Endocrinol* 294(1-2): 81-91.
 11. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, et al. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 142(5): 687-698.